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Placenta accreta in Australia and New Zealand: A case-control study

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Title: Placenta accreta in Australia and New Zealand: A case-control study

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ABSTRACT

Objective Estimate the incidence of placenta accreta and describe risk factors, clinical management and perinatal outcomes.

Design Case-control study.

Setting Sites in Australia and New Zealand with at least 50 births per year

Participants Cases were defined as women giving birth (≥20 weeks or fetus ≥400g) who were diagnosed with placenta accreta by either antenatal imaging, at operation or by pathology specimens from 2010-2012. Controls were two births immediately prior to a case. A total of 295 cases were included and 570 controls.

Methods Data were collected using the Australasian Maternity Outcomes Surveillance System.

Primary and secondary outcome measures: Incidence, risk factors (e.g. prior caesarean section (CS), maternal age) and clinical outcomes of placenta accreta (e.g. CS, hysteroscopy, intensive care admission, death).

Results The incidence of placenta accreta was 44.2/100,000 women giving birth (95% CI: 39.4 - 49.5). In primiparous women, an increased odds of placenta accreta was observed in older women (AOR women ≥40 vs. <30: 19.1, 95% CI: 4.6-80.3), and current multiple birth (AOR: 6.1, 95% CI 1.1-34.1). In multiparous women, independent risk factors were prior CS (AOR ≥2 prior sections vs. 0: 13.8, 95% CI: 7.4-26.1), and current placenta praevia (AOR: 36.3, 95% CI: 14.0 – 93.7). There were 2 maternal deaths (case fatality rate 0.7%).

Women with placenta accreta were more likely to have a caesarean section (AOR: 4.6, 95% CI: 2.7 – 7.6), to be admitted to the ICU/HDU (AOR: 46.1, 95% CI: 22.3 – 95.4), and to have a hysterectomy (AOR: 209.0, 95% CI: 19.9 – 875.0). Babies born to women with placenta

accreta were more likely to be preterm, have low birthweight, be admitted to NICU, and require resuscitation.

Conclusions Placenta accreta is associated with a high risk of severe morbidity, peripartum hysterectomy and in a minority of cases, maternal death.

Key words: caesarean, c-section, placenta accreta, placentation

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first national case-control study of placenta accreta in Australia and New Zealand
- This case control study used active negative surveillance by detected researchers, limiting recall bias and errors common in administrative datasets
- This study may have included cases which were diagnosed antenatally, but which were not confirmed clinically at operation or on pathology and therefore not true cases of placenta accreta
- Denominator data for the number of births in Australian hospitals is an estimate because of the varying start time for hospitals in the study.

INTRODUCTION

Placenta accreta is an uncommon condition occurring during pregnancy which is characterized by abnormal placentation. The severity of abnormal placentation can be classified into three grades based on histopathology: the least severe and most common presentation is placenta accreta, in which the placental villi penetrate only to the surface of the myometrium. Placenta increta is characterized by invasion of placental villi into the myometrium. The most severe form is placenta percreta, characterized by invasion of villi beyond the myometrium to the uterine serosa, and in some cases involving adjacent organs such as the bladder.[1] The term 'placenta accreta' refers to all three conditions in this paper. Placenta accreta is associated with major pregnancy complications such as massive blood loss and hysterectomy, and is potentially life-threatening. Once the diagnosis of placenta accreta is established, the decision about mode of birth requires multidisciplinary team planning, and often involves complex surgery or radiological interventions to reduce maternal and neonatal morbidity.[2, 3]

The incidence of placenta accreta is believed to be increasing globally.[2, 3] This is likely attributable to an increase in caesarean sections and trends towards older women giving birth, both of which are independent risk factors for placenta accreta.[4, 5] There are a growing number of caesarean sections in Australia and New Zealand,[6] however the epidemiology and management of placenta accreta in these countries has not been previously reported. As the prevalence of risk-factors for this condition may be different in the Australian and New Zealand population, such as the prevalence of previous caesarian births, the aim of this study was to estimate the incidence of placenta accreta in these countries, and to describe risk factors, clinical management and outcomes, for women affected by this condition and their babies.

MATERIALS AND METHODS

A bi-national population-based case-control study was undertaken using the research platform of the Australasian Maternity Outcomes Surveillance System (AMOSS). AMOSS was established across maternity units in Australia and New Zealand in 2009 to study rare and serious disorders of pregnancy.[7, 8] Data were collected from participating sites, which were public and private maternity units with more than 50 births per year in Australia and New Zealand, incorporating all service levels. Australian sites (n = 269) progressively joined AMOSS on completion of relevant ethics and governance approvals. In New Zealand, all 24 maternity units participated (100% of hospital births).[8]

Women were identified by AMOSS-participating sites from January 2010 to December 2011 (Australia) and to December 2012 (New Zealand). Nominated clinicians and midwives were contacted each month using an active negative surveillance system. The average monthly response rate was 91%. Cases were defined as: women giving birth who were diagnosed with placenta accreta by either antenatal imaging, at operation or by pathology specimens. The type of diagnosis was re-coded according to the earliest diagnosis. For example, a case diagnosed both by antenatal imaging and by pathology specimen was coded as diagnosed by antenatal imaging. Giving birth was defined as the birth of one or more live or stillborn infants of at least 400 g birthweight and/or at least 20 weeks' gestation.[9, 10] The two women giving birth immediately prior to the case in the same hospital were selected as controls.

Data were collected using secure, web-based forms which captured general demographic and pregnancy data, and case-specific information about prior obstetric history, current pregnancy, and placenta accreta diagnosis and management, such as use of hysterectomy. For controls, the outcome of hysterectomy was obtained from a free-text field on maternal morbidity, and by probabilistic matching against the AMOSS hysterectomy cohort.

Data collectors at participating hospitals were contacted regarding missing data or where data were not consistent with expected values. Logic checks were run on the data to identify

any impossible or improbable scenarios. Free text responses to questions regarding medical or obstetric morbidity were classified according to ICD-10-Australian Modification. All data were collected in a non-identifiable manner.

Ethics approval for AMOSS was granted by the NSW Population and Health Services Research Ethics Committee and multiple Human Research Ethics Committees across Australia and the multiregional ethics approval (MEC/09/73/EXP) in New Zealand.[11]

After adjusting for the phased implementation of AMOSS, there were an estimated 478,820 women giving birth (486,003 babies born) in Australia and 189,116 (190,408 babies born) in New Zealand across the participating maternity sites during the study period. In New Zealand these denominators were calculated from the Ministry of Health data.[12-14] and in Australia by using the number of days' participation in the study multiplied by number of births per day for that hospital, which gave approximate coverage ranging from 75% in 2010 to 82% in 2011 of all women giving birth in Australia, respectively. Incidence rates were calculated with 95% confidence intervals (CI). Fisher's exact test, Chi-square test, independent samples t-test and Mann–Whitney U-test were used to investigate differences in demographics and obstetric characteristics, maternal and perinatal outcomes between cases and the controls. Multivariate logistic regression was used to examine the risk factors for placenta accreta and to compare the maternal and perinatal outcomes of cases and controls. Odds ratio (OR), adjusted odds ratio (AOR) and 95% CI were calculated. Adjustment was made for maternal age, body mass index (BMI), smoking status during pregnancy, number of previous caesarean deliveries, placenta praevia during pregnancy, multiple pregnancies, and assisted reproductive technologies. Data were analysed using the Statistical Package for the Social Sciences software, version 22.0 (IBM Corporation, Somers, NY, USA).

RESULTS

Of the 308 cases notified to AMOSS, 295 were eligible after excluding 13 cases; seven outside the study period, three duplicate notifications, and three not satisfying the birth

definition. Of the 295 cases, 227 women were from Australia and 68 from New Zealand. Data were available for 570 controls, as the data for 20 controls was missing.

The incidence of placenta accreta for the study period was 44.2/100,000 women giving birth (95% CI: 39.4 - 49.5). The incidences in Australia and New Zealand were 47.4/100,000 (95% CI: 41.6- 54.0) and 36.0/100,000 (95% CI: 28.4-45.6) respectively. There were 12 perinatal deaths among the cases (perinatal death rate 38.7 per 1,000 births) and 10 among the controls (perinatal death rate 17.2 per 1,000 births). There were two maternal deaths among the cases, resulting in a case fatality rate of 0.7%. The causes of death were cerebrovascular accident secondary to pulmonary embolism, and catastrophic postpartum haemorrhage due to placenta accreta. There were no maternal deaths among controls.

Almost half of the cases were diagnosed by antenatal imaging (143, 48.5%), 132 (44.7%) were first diagnosed clinically at operation, and 16 (5.4%) were not diagnosed until histological confirmation following delivery; in four cases the time of diagnosis was not reported. There were 213 (72.2%) cases with placenta accreta, 37 (12.5%) with placenta increta and 45 (15.3%) with placenta percreta.

The median age of women with placenta accreta was 35 years (range 21-55) and the median BMI was 28kg/m2 (range 16.3-57.8) (Table 1). Over 80% of cases had a previous birth and 68% had a previous caesarean section. Eight percent of pregnancies among the cases were conceived following assisted reproductive technologies and 5% of the cases had current multiple pregnancies. Forty four percent of cases also had placenta praevia diagnosed prior to the birth (Table 1).

Women with placenta accreta were more likely to be older, have a higher BMI, a previous birth, previous caesarean section, placenta praevia diagnosed prior to delivery, current multiple pregnancy, and to have conceived following assisted reproductive technologies (Table 1).

Multivariate analysis was conducted separately for primiparous and multiparous women, as

previous caesarean section is only applicable to women with a previous birth. In primiparous women, maternal age remained an independent risk factor for placenta accreta; mothers 40 or over had more than a 19-fold higher odds of placenta accreta compared to young mothers aged less than 30 (Table 2). The presence of a current multiple pregnancy was also a risk factor for placenta accreta in primiparous women (AOR: 6.1, 95% CI 1.1-34.1). In multiparous women, the independent risk factors were prior caesarean section (AOR ≥2 prior sections vs. 0: 13.8, 95% CI: 7.4-26.1) and current placenta praevia (AOR: 36.3, 95% CI: 14.0 – 93.7).

As the management of cases is expected to differ according to the knowledge of a placenta accreta, the cases were categorized by whether or not the placenta accreta was suspected prior to birth (Table 3). Of the cases, 169 (57.3%) had a placenta accreta suspected prior to birth. On average, women with a suspected placenta accreta had a more severe condition; 57 (33%) of suspected cases had a placenta increta or percreta, compared to 24 (19.5%) of non-suspected cases.

Cases were less likely to labour than controls (20% vs 79%); the majority of cases who labored had an unsuspected placenta accreta. Additionally, cases were more likely to: give birth at an earlier gestation, to have a caesarean section, to be admitted to a high dependency unit (HDU) and to have a hysterectomy. Two-thirds of cases (196/295; 66%) underwent hysterectomy compared with only two controls (2/570; 0.3%). In the two controls that required a hysterectomy, the underlying cause of hemorrhage was uterine atony. Of cases undergoing hysterectomy, 15 (7.7%) had no previous birth.

After adjusting for confounding factors, cases remained more likely to have a caesarean delivery (AOR: 4.6, 95% CI: 2.7 – 7.6), to be admitted to the intensive care unit (ICU)/HDU (AOR: 46.1, 95% CI: 22.3 – 95.4), and to have a hysterectomy (AOR: 209.0, 95% CI: 19.9 – 875.0). These analyses were adjusted for maternal age, BMI, smoking, number of previous caesarean sections, placenta praevia diagnosed prior to delivery, multiple pregnancy, and use of assisted reproductive technologies.

Babies born to mothers with placenta accreta were more likely to be preterm (mean gestational age at birth 36 vs. 39 weeks), and have lower birthweights, with 40% vs. 9% of babies born weighing 2500g or less (Table 4). These babies were also more likely to have an Apgar score of 7 or less five minutes after birth, require resuscitation and to be admitted to a neonatal intensive care unit (NICU). Among cases, there was a higher chance of being discharged to another health facility and of neonatal death.

In the multivariate analysis, the following baby's outcomes remained significantly associated with placenta accreta: preterm birth: (AOR: 5.0 95% CI: 3.2 – 7.8), low birthweight: (AOR: 5.0, 95% CI: 2.9 – 8.4), admission to NICU: (AOR: 4.4, 95% CI: 2.8 – 6.9), Apgar 5min <7: (AOR: 7.8, 95% CI: 3.1 – 19.9), resuscitation required: (AOR: 4.5, 95% CI: 2.7 – 7.4) (Table 4). These analyses included singleton births only and were adjusted for maternal age, BMI, smoking, number of previous caesarean sections, placenta praevia diagnosed prior to delivery, and assisted reproductive technologies.

COMMENT

The incidence of placenta accreta identified in this study was 44.2/100,000 women giving birth. This is similar to the rates reported previously from single-centre studies in individual hospitals in New Zealand (60.2/100,000),[15] and Australia (38.8/100,000).[16] This paper is the first to report on the national incidence of placenta accreta in both Australia and New Zealand.

The rates of placenta accreta reported previously vary markedly, both across geographic populations and as a result of different definitions of 'placenta accreta'. The highest incidence has been reported in Israel at 900/100,000,[17] and a lower rate of 40/100,000 has been reported in the United States of America.[18] A review including 34 studies reported an average incidence of 189/100,000.[4] More recently the incidence of placenta accreta reported in the national United Kingdom Obstetric Surveillance System (UKOSS), was 17/100,000 women giving birth, from cases collected over a 12 month period in 2010-2011.[19] Both UKOSS and AMOSS are case-control studies that employed national active

negative surveillance of cases. The UKOSS methods defined placenta accreta as "diagnosed histologically following hysterectomy or post-mortem or an abnormally adherent placenta, requiring active management, including conservative approaches where the placenta is left in situ" whereas this study also included cases of diagnosis by antenatal imaging. It is possible that some cases included in this study were diagnosed at antenatal imaging and not found to have placenta accreta at the time of birth, which is not uncommon.[3, 20] Therefore this study may have overestimated the true incidence of placenta accreta. It is also possible that the difference is a result of different exposure to risk factors. There appears to be a higher proportion of control women with risk factors for placenta accreta among the AMOSS cohort, for example rates of prior caesarean section (18% vs 15%), pregnancy conceived from assisted reproductive technologies (2.6% vs 1%), and maternal age of 35 or older (27% vs 24%).

This study reports four independent risk factors for placenta accreta: older maternal age, prior caesarean section, placenta praevia diagnosed prior to birth, and multiple birth; which have also been reported by other studies.[4, 21-23] Previous studies have also reported risk factors that this study did not find to be independent, specifically: smoking,[24] use of assisted reproductive technologies,[25] and sex of fetus.[26] Risk factors reported previously which were not measured in this study include hypertensive disorders, previous uterine surgery,[17, 27] elevated second-trimester serum levels of AFP and free β-hCG.[26]

Although the case definition establishes the outcome of this study as placenta accreta, it is important to consider the consequences of this condition for mother and baby. The maternal case fatality rate was 7/1000, with no maternal deaths among controls. The perinatal mortality rate was 39/1000 births for cases and 17/1000 births for controls. This is slightly higher than reported previously in this population, and may be a result of the small numbers of deaths in this cohort (10/582), and the identification of controls as those delivering at the same hospital as cases, which are more likely to be tertiary hospitals.[9]

Maternal morbidity is high among women with placenta accreta. Just over one third of cases

(35%) were admitted to the ICU or HDU, compared to less than 2% of controls. Two thirds of cases underwent a hysterectomy (66.4%) compared to only 0.4% of controls. Hysterectomy can be a devastating outcome for women wishing to expand their families, and is itself a significant operation. In this study, 42% of cases had an unsuspected placenta accreta and 43% of these had an unplanned hysterectomy. Of cases undergoing a hysterectomy, 92.3% had at least one baby previously, compared to 69% having had a prior birth among cases who did not undergo a hysterectomy. This may reflect a higher incidence of placenta accreta in women with previous births, older maternal age, and a stronger motivation to retain the uterus in women undergoing their first birth.

Women with placenta accreta were more likely to give birth earlier and consequently the babies born to these women were more often preterm, low birthweight, required resuscitation, admitted to NICU, and were more likely to die. Women with a suspected placenta accreta had a 74.7% preterm birth rate; however the preterm birth rate was also much higher among those with an unsuspected placenta accreta compared to controls (37.6% vs 13.2%). Other studies have also reported higher preterm delivery rates and poorer outcomes for babies born to mothers with placenta accreta.[28] However this study did not find a higher rate of small for gestational age babies among women with placenta accreta, which has been inconsistently reported in other studies.[4, 29]

It appears that women and babies with a suspected placenta accreta had inferior outcomes than those with an unknown placenta accreta, for example higher rates of premature birth, hysterectomy, and admission to ICU/HDU. This possibly reflects the higher index of suspicion around more severe cases, for example one third of suspected cases were diagnosed with a more severe form of placenta accreta (increta or percreta) compared to 19.5% of unsuspected cases.

The major strength of the AMOSS study design is the active negative surveillance for cases. Cases were captured as they occurred which minimized the risk of recall bias compared to traditional case-control studies. Although the case ascertainment is believed to be high, it is

not possible to be sure of the exact level of ascertainment achieved. The study audited clinical records and did not solely depend on administrative datasets which are often unreliable, particularly for uncommon conditions.

A possible limitation of this study relates to the possible inclusion of cases which were diagnosed antenatally, but which were not confirmed clinically at operation or on pathology; however this reflects diagnosis in real practice. Further, as it was not possible to assess how many of these cases were included, it was not possible to estimate the probability of misdiagnosis and consequent avoidable morbidity from unnecessary caesarean section. The inclusion criteria was women giving birth, defined as at least 400 g birthweight and/or at least 20 weeks' gestation. Therefore any cases of accreta that resulted in an early second trimester miscarriage were not included; however the number of these cases is expected to be few. Additionally, denominator data for the number of births in Australian hospitals is an estimate because of the varying start time for hospitals in the study.

Future research could explore the role of antenatal diagnosis and screening of women with risk factors for placenta accreta. A significant proportion of the cases in this study had an unsuspected placenta accreta, and nearly half of these underwent an unplanned hysterectomy. This is despite routine ultrasound for assessment of the placenta at approximately 20 weeks' gestation in these countries.

This national study from Australia and New Zealand confirms the incidence of placenta accreta in this high income setting at approximately one in two thousand women giving birth. Although the condition remains rare, it is associated with a high risk of severe morbidity, and in a minority of cases, maternal death. The independent risk factors for placenta accreta in primiparous women were advanced maternal age and current multiple pregnancy. In multiparous women, previous caesarean birth and current placenta praevia were associated with an increased risk of placenta accreta. Further research on the role of antenatal diagnosis and screening in women with risk factors, particularly previous caesarean delivery, is warranted to inform clinical decision making about place and mode of birth, and to

minimize risk of maternal and perinatal morbidity and mortality.

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CONTRIBUTION TO AUTHORSHIP

CF, MP ES, CM, WP, DE, MK, CH conceptualized and designed the study protocol and case report forms. GV. ES managed data collection and oversaw operational aspects of the study. SL, ZL, ES, CF devised the data analysis. ZL, AW undertook the data analysis. CF, SL, ES and ZL led the drafting of the paper. All authors revised the manuscript and approved the final draft.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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DATA SHARING STATEMENT

No additional data are available.

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Table 1 Demographics and obstetric characteristics

	Case	Control	p-value
	N(%)	N(%)	
Total	295(100.0)	570(100.0)	
Country			
Australia	227(76.9)	436(76.5)	0.88
New Zealand	68(23.1)	134(23.5)	
Maternal age			
< 25	7(2.4)	93(16.3)	
25-29	44(14.9)	147(25.8)	
30-34	94(31.9)	177(31.1)	<0.001
35-39	112(38.0)	121(21.2)	
≥40	38(12.9)	32(5.6)	
Indigenous status (Australian only)			
Yes	11(4.8)	13(3.0)	0.206
No	202(89.0)	403(92.4)	
Not stated	14(6.2)	20(4.6)	
Ethnicity (New Zealand only)			
Maori	13(19.1)	18(13.4)	
New Zealand European	34(50.0)	63(47.0)	0.34
Pacific Peoples	5(7.4)	17(12.7)	
Other	12(17.6)	34(25.4)	
Not stated	4(5.9)	2(1.5)	
Body Mass Index (kg/m^2)			
<25	115(39.0)	272(47.7)	
25-29.9	66(22.4)	128(22.5)	<0.05
≥30	78(26.4)	112(19.6)	
Not stated	36(12.2)	58(10.2)	
Smoking during pregnancy			
Yes	56(19.0)	97(17.0)	0.45
No	215(72.9)	429(75.3)	
Not stated	24(8.1)	44(7.7)	
Parity			
0	46(15.6)	240(42.1)	
1-2	159(53.9)	274(48.1)	<0.001
≥3	90(30.5)	56(9.8)	
Number of previous caesarean deliveries			
No prior caesarean delivery	43(14.6)	225(39.5)	
1	89(30.2)	80(14.0)	
2	62(21.0)	19(3.3)	<0.001
≥3	50(16.9)	3(0.5)	
Not applicable (no prior births)	46(15.6)	240(42.1)	
Not stated	5(1.7)	3(0.5)	
Last pregnancy delivery by caesarean delivery			
Yes	188(63.7)	91(16.0)	<0.001

No	55(18.6)	234(41.1)	
Not applicable (no prior births)	46(15.6)	240(42.1)	
Not stated	6(2.0)	5(0.9)	
Placenta praevia during pregnancy			
Yes	130(44.1)	8(1.4)	<0.001
No	165(55.9)	562(98.6)	
Multiple pregnancy			
Yes	15(5.1)	13(2.3)	<0.05
No	280(94.9)	555(97.4)	
Not stated	0(0.0)	2(0.4)	
Assisted conception			
Yes	24(8.1)	15(2.6)	<0.001
No	259(87.8)	521(91.4)	
Not stated	12(4.1)	34(6.0)	

Table 2 Risk factor analysis

	Primiparous women		Multiparous women	
	OR (95% CI)	AOR (95% CI)*	OR (95% CI)	AOR (95% CI)†
Maternal age				
< 30	Ref	Ref	Ref	Ref
30-34	8.0(2.6-24.9)	6.3(2.0-20.0)	1.7(1.-,2.7)	1.7(0.9-3.2)
35-39	11.0(3.5-34.9)	7.0(2.1-23.6)	3.1(2.0-4.8)	2.7(1.4-5.2)
≥40	30.7(8.2-115.9)	19.1(4.6-80.3)	3.1(1.6-6.0)	2.0(0.8-5.0)
Body Mass Index (kg/m^2)				
<25	Ref	Ref	Ref	Ref
25-29.9	1.2(0.6-2.6)	1.4(0.6-3.2)	1.1(0.7-1.8)	0.8(0.4-1.4)
≥30	0.7(0.3-2.0)	0.7(0.2-2.2)	1.4(0.9-2.1)	0.8(0.5-1.4)
Smoking during pregnancy	0.2(0.1-1.0)	0.4(0.1-1.8)	1.3(0.9-2.0)	1.3(0.7-2.4)
Number of previous caesarean deliveries				
No prior caesarean delivery	n.a	n.a	Ref	Ref
1	n.a	n.a	5.8(3.7-9.1)	3.7(2.2-6.3)
≥2	n.a	n.a	24.8(14.3-43.1)	13.8(7.4-26.1)
Placenta praevia during pregnancy	9.6(2.2-41.9)	3.0(0.6-15.2)	64.9(25.9-162.5)	36.3(14.0-93.7)
Multiple pregnancy	14.2(3.5-57.2)	6.1(1.1-34.1)	1.1(0.4-2.7)	1.5(0.5-4.9)
Assisted conception	5.4(2.2-13.1)	1.5(0.5-5.1)	4.4(1.4-13.7)	2.6(0.6-11.2)

*Adjusted for maternal age, body mass index, smoking, placenta praevia during pregnancy, multiple pregnancy, and assisted conception

†Adjusted for maternal age, body mass index, smoking, number of previous caesarean deliveries, placenta praevia during pregnancy, multiple pregnancy, and assisted conception

OR: odds ratio, AOR: adjusted odds ratio, Ref: reference value, n.a: not applicable

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Table 3 Labour, birth and maternal morbidity

	Case			Control (n=570)	p-value†
	PA suspected antenatally (n=169)	PA **not** suspected antenatally (n=123)	Total* (n=295)		
	N(%)	N(%)	N(%)	N(%)	
Did the woman labour					
Yes	7(4.1)	51(41.5)	59(20.0)	451(79.1)	<0.001
No	162(95.9)	72(58.5)	236(80.0)	117(20.5)	
Not stated	0(0.0)	0(0.0)	0(0.0)	2(0.4)	
Induced labour					
Yes	1(14.3)	16(31.4)	17(28.8)	116(25.7)	0.545
No	5(71.4)	34(66.7)	40(67.8)	329(72.9)	
Not stated	1(14.3)	1(2.0)	2(3.4)	6(1.3)	
Gestation at delivery, weeks, median	35.0	38.0	36.0	39.0	<0.001
Method of birth					
Unassisted vaginal birth	1(0.6)	30(24.4)	31(10.5)	314(55.1)	
Instrumental vaginal birth	0(0.0)	5(4.1)	5(1.7)	71(12.5)	
Planned caesarean delivery	140(82.8)	50(40.7)	190(64.4)	107(18.8)	<0.001
Unplanned caesarean delivery	28(16.6)	38(30.9)	69(23.4)	77(13.5)	
Not stated	0(0.0)	0(0.0)	0(0.0)	1(0.2)	
Admission to ICU					
Yes	65(38.5)	40(32.5)	105(35.6)	6(1.1)	<0.001
No	104(61.5)	81(65.9)	188(63.7)	564(98.9)	
Not stated	0(0.0)	2(1.6)	2(0.7)	0(0.0)	
Admission to HDU					
Yes	68(40.2)	32(26.0)	101(34.2)	8(1.4)	<0.001
No	100(59.2)	89(72.4)	191(64.7)	562(98.6)	
Not stated	1(0.6)	2(1.6)	3(1.0)	0(0.0)	
Had hysterectomy					
Yes	142(84.0)	53(43.1)	196(66.4)	2(0.4)	<0.001
No	27(16.0)	69(56.1)	98(33.2)	568(99.6)	
Not stated	0(0.0)	1(0.8)	1(0.3)	0(0.0)	
Maternal death					
Yes	1(0.6)	1(0.8)	2(0.7)	0(0.0)	0.116
No	168(99.4)	122(99.2)	293(99.3)	570(100.0)	

PA: placenta accreta, ICU: intensive care unit; HDU: high dependency unit

* Includes 3 cases where it was not known whether PA was suspected prior to delivery.

† Total number of cases vs control.

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Table 4 Perinatal morbidity

	Case			Control (n= 582)	p-value†
	PA suspected antenatally (n= 174)	PA not suspected antenatally (n= 133)	Total* (n= 310)		
	N(%)	N(%)	N(%)	N(%)	
Fetal deaths	5(2.9)	4(3.0)	9(2.9)	5(0.9)	<0.05
Perinatal deaths	7(4.0)	5(3.8)	12(3.9)	10(1.7)	<0.05
Sex					
Male	87(50.0)	55(41.4)	142(45.8)	282(48.5)	0.525
Female	84(48.3)	78(58.6)	165(53.2)	298(51.2)	
Not stated	3(1.7)	0(0.0)	3(1.0)	2(0.3)	
Gestational age, weeks, median	35.0	38.0	36.0	39.0	<0.001
Preterm birth (<37 weeks)					
Yes	130(74.7)	50(37.6)	183(59.0)	77(13.2)	<0.001
No	43(24.7)	83(62.4)	126(40.6)	503(86.4)	
Not stated	1(0.6)	0(0.0)	1(0.3)	2(0.3)	
Birthweight*, g, mean	2468.3(±709.1)	2870.0(±847.8)	2640.3(±795.8)	3281.4(±615.8)	<0.001
Low birthweight *(<2500g)					
Yes	81(48.5)	38(29.5)	120(40.1)	54(9.4)	<0.001
No	85(50.9)	88(68.2)	175(58.5)	517(89.6)	
Not stated	1(0.6)	3(2.3)	4(1.3)	6(1.0)	
Small for gestational age*					
Yes	8(4.8)	14(10.9)	22(7.4)	55(9.5)	0.287
No	158(94.6)	112(86.8)	273(91.3)	516(89.4)	
Not stated	1(0.6)	3(2.3)	4(1.3)	6(1.0)	
Admission to NICU*					
Yes	130(77.8)	51(39.5)	183(61.2)	90(15.6)	<0.001
No	36(21.6)	76(58.9)	113(37.8)	479(83.0)	
Not stated	1(0.6)	2(1.6)	3(1.0)	8(1.4)	
Apgar score at 5 minutes*					
<7	59(35.3)	7(5.4)	66(22.1)	9(1.6)	<0.001
7-10	106(63.5)	120(93.0)	229(76.6)	559(96.9)	
Not stated	2(1.2)	2(1.6)	4(1.3)	9(1.6)	
Resuscitation*					
Yes	99(59.3)	29(22.5)	130(43.5)	49(8.5)	<0.001
No	65(38.9)	96(74.4)	162(54.2)	520(90.1)	
Not stated	3(1.8)	4(3.1)	7(2.3)	8(1.4)	
Separation status*					
Discharged home	119(71.3)	111(86.0)	232(77.6)	542(93.9)	
Transferred to another health facility/other	41(24.6)	16(12.4)	58(19.4)	28(4.9)	<0.001
Neonatal death	2(1.2)	1(0.8)	3(1.0)	5(0.9)	
Not stated	5(3.0)	1(0.8)	6(2.0)	2(0.3)	

*Live births only

†case vs control

PA: placenta accreta, NICU: neonatal intensive care unit

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – line 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – see Abstract
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – - see Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses - see Introduction lines 100-104
Methods		
Study design	4	Present key elements of study design early in the paper – see start of Methods
Setting	5	Describe the setting (lines 110-114), locations (lines 110-114), and relevant dates including periods of recruitment (lines 115-116), exposure (lines 115-116), follow-up (lines 115-116), and data collection (lines 115-116)
Participants	6	(*a*) Give the eligibility criteria (lines 118-125), and the sources and methods of case ascertainment and control selection (lines 118-125). Give the rationale for the choice of cases and controls
		(*b*) For matched studies, give matching criteria and the number of controls per case NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable - see Methods and Results
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group - see Methods and Results
Bias	9	Describe any efforts to address potential sources of bias - see lines 291-306
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why - see lines 141-156
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding- see lines 141-156
		(*b*) Describe any methods used to examine subgroups and interactions - see lines 141-156
		(*c*) Explain how missing data were addressed - see lines 141-156
		(*d*) If applicable, explain how matching of cases and controls was addressed NA
		(*e*) Describe any sensitivity analyses NA
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed - see lines 158-161
		(b) Give reasons for non-participation at each stage NA
		(c) Consider use of a flow diagram NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – Table 1
		(b) Indicate number of participants with missing data for each variable of interest

Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure – Tables
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – all through Results
		(*b*) Report category boundaries when continuous variables were categorized – See Tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – See Tables and Results
Discussion		
Key results	18	Summarise key results with reference to study objectives – first half of Comment section
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – see lines 291-306
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results – start of Comment
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - reported

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Placenta accreta in Australia and New Zealand: A case-control study

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Title: Placenta accreta in Australia and New Zealand: A case-control study

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ABSTRACT

Objective Estimate the incidence of placenta accreta and describe risk factors, clinical practice and perinatal outcomes.

Design Case-control study.

Setting Sites in Australia and New Zealand with at least 50 births per year

Participants Cases were defined as women giving birth (≥20 weeks or fetus ≥400g) who were diagnosed with placenta accreta by either antenatal imaging, at operation or by pathology specimens between 2010-2012. Controls were two births immediately prior to a case. A total of 295 cases were included and 570 controls.

Methods Data were collected using the Australasian Maternity Outcomes Surveillance System.

Primary and secondary outcome measures: Incidence, risk factors (e.g. prior caesarean section (CS), maternal age) and clinical outcomes of placenta accreta (e.g. CS, intensive care admission, hysterectomy, and death).

Results The incidence of placenta accreta was 44.2/100,000 women giving birth (95% CI: 39.4 - 49.5). In primiparous women, an increased odds of placenta accreta was observed in older women (AOR women ≥40 vs. <30: 19.1, 95% CI: 4.6-80.3), and current multiple birth (AOR: 6.1, 95% CI 1.1-34.1). In multiparous women, independent risk factors were prior CS (AOR ≥2 prior sections vs. 0: 13.8, 95% CI: 7.4-26.1), and current placenta praevia (AOR: 36.3, 95% CI: 14.0 – 93.7). There were 2 maternal deaths (case fatality rate 0.7%).

Women with placenta accreta were more likely to have a caesarean section (AOR: 4.6, 95% CI: 2.7 – 7.6), to be admitted to the ICU/HDU (AOR: 46.1, 95% CI: 22.3 – 95.4), and to have a hysterectomy (AOR: 209.0, 95% CI: 19.9 – 875.0). Babies born to women with placenta

accreta were more likely to be preterm, have low birthweight, be admitted to NICU, and require resuscitation.

Conclusions Placenta accreta is associated with a high risk of severe morbidity, peripartum hysterectomy and in a minority of cases, maternal death.

Key words: caesarean, c-section, placenta accreta, placentation

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first national and bi-national case-control study of placenta accreta in Australia and New Zealand
- This case control study used active negative surveillance of cases by dedicated researchers, limiting recall bias and errors common in administrative datasets
- This study may have included cases which were diagnosed antenatally, but which were not confirmed clinically at operation or on pathology and therefore not true cases of placenta accreta
- Denominator data for the number of births in Australian hospitals is an estimate because of the varying start time for hospitals in the study.

INTRODUCTION

Placenta accreta is an uncommon condition occurring during pregnancy which is characterized by abnormal placentation. The severity of abnormal placentation can be classified into three grades based on histopathology: the least severe and most common presentation is placenta accreta, in which the placental villi penetrate only to the surface of the myometrium. Placenta increta is characterized by invasion of placental villi into the myometrium. The most severe form is placenta percreta, characterized by invasion of villi beyond the myometrium to the uterine serosa, and in some cases involving adjacent organs such as the bladder.[1] The term 'placenta accreta' refers to all three conditions in this paper. Placenta accreta is associated with major pregnancy complications such as massive blood loss and hysterectomy, and is potentially life-threatening. Once the diagnosis of placenta accreta is established, the decision about mode of birth requires multidisciplinary team planning, and often involves complex surgery or radiological interventions to reduce maternal and neonatal morbidity.[2, 3]

The incidence of placenta accreta is believed to be increasing globally.[2, 3] This is likely attributable to an increase in caesarean sections and trends towards older women giving birth, both of which are independent risk factors for placenta accreta.[4, 5] There are a growing number of caesarean sections in Australia and New Zealand,[6] however the epidemiology and clinical practices for managing placenta accreta in these countries has not been previously reported. The prevalence of risk-factors for this condition may be different in the Australian and New Zealand population, such as the prevalence of previous caesarian births. A case-control study with active negative surveillance was undertaken with the aim of estimating the incidence of placenta accreta in Australia and New Zealand, and describing risk factors, clinical practices and outcomes, for women affected by this condition and their babies.

MATERIALS AND METHODS

A bi-national population-based case-control study was undertaken using the research platform of the Australasian Maternity Outcomes Surveillance System (AMOSS). AMOSS was established across maternity units in Australia and New Zealand in 2009 to study rare and serious disorders of pregnancy.[7, 8] There were six studies conducted contemporaneously including studies on: amniotic fluid embolism, antenatal pulmonary embolism, eclampsia, super-obesity and peripartum hysterectomy, which used a similar study design and data collection methodology. Data were collected from participating sites, which were public and private maternity units with more than 50 births per year in Australia and New Zealand, incorporating all service levels. Australian sites (n = 269) progressively joined AMOSS on completion of relevant ethics and governance approvals. In New Zealand, all 24 maternity units participated (100% of hospital births).[8]

Women were identified by AMOSS-participating sites from January 2010 to December 2011 (Australia), and to December 2012 (New Zealand). All AMOSS hospital-based data collectors received study information on the surveillance period, recruitment, case definition, and inclusion and exclusion criteria. Central support was available for local data collectors, including confirmation that individual cases satisfied the inclusion criteria. Nominated clinicians and midwives were contacted each month using an active negative surveillance system, querying whether a case had occurred that month. Data collectors identified cases through multiple sources: review of routine data collection within the hospital, audit committees, clinician notification and request to clinicians of potential cases. The average monthly response rate was 91%.

Cases were defined as: women giving birth who were diagnosed with placenta accreta by either antenatal imaging, at operation or by pathology specimens. The type of diagnosis was re-coded according to the earliest diagnosis. For example, a case diagnosed both by antenatal imaging and by pathology specimen was coded as diagnosed by antenatal imaging. Giving birth was defined as the birth of one or more live or stillborn infants of at

least 400 g birthweight and/or at least 20 weeks' gestation.[9, 10] The two women giving birth immediately prior to the case in the same hospital were selected as controls. Perinatal deaths included fetal deaths of at least 400 g birthweight or 20 weeks' gestation, and neonatal deaths occurring within 28 days after birth.

Data were collected using secure, web-based forms which captured general demographic and pregnancy data, and case-specific information about prior obstetric history, current pregnancy, and placenta accreta diagnosis and clinical practice, such as use of hysterectomy. For controls, the outcome of hysterectomy was obtained from a free-text field on maternal morbidity, and by probabilistic matching against the AMOSS hysterectomy cohort.

Data collectors at participating hospitals were contacted regarding missing data or where data were not consistent with expected values. Logic checks were run on the data to identify any impossible or improbable scenarios. Free text responses to questions regarding medical or obstetric morbidity were classified according to ICD-10-Australian Modification. All data were collected in a non-identifiable manner.

Ethics approval for AMOSS was granted by the NSW Population and Health Services Research Ethics Committee and multiple Human Research Ethics Committees across Australia and the multiregional ethics approval (MEC/09/73/EXP) in New Zealand.[11]

After adjusting for the phased implementation of AMOSS, there were an estimated 478,820 women giving birth (486,003 babies born) in Australia and 189,116 (190,408 babies born) in New Zealand across the participating maternity sites during the study period. In New Zealand these denominators were calculated from the Ministry of Health data, [12-14] and in Australia by using the number of days' participation in the study multiplied by number of births per day for that hospital, which gave approximate coverage ranging from 75% in 2010 to 82% in 2011 of all women giving birth in Australia, respectively. Incidence rates were calculated with 95% confidence intervals (CI). Fisher's exact test, Chi-square test, independent samples t-test and Mann–Whitney U-test were used to investigate differences in demographics and obstetric characteristics, maternal and perinatal outcomes between

cases and the controls. Multivariate logistic regression was used to examine the risk factors for placenta accreta by parity, and to compare the maternal and perinatal outcomes of cases and controls. Odds ratio (OR), adjusted odds ratio (AOR) and 95% CI were calculated. Adjustment was made for maternal age, body mass index (BMI), smoking status during pregnancy, parity, number of previous caesarean births, placenta praevia during pregnancy, multiple pregnancies, and assisted reproductive technologies. Data were analysed using the Statistical Package for the Social Sciences software, version 22.0 (IBM Corporation, Somers, NY, USA).

RESULTS

Of the 308 cases notified to AMOSS, 295 were eligible after excluding 13 cases; seven outside the study period, three duplicate notifications, and three not satisfying the birth definition. Of the 295 cases, 227 women were from Australia and 68 from New Zealand. Data were available for 570 controls, as the data for 20 controls was missing.

The incidence of placenta accreta for the study period was 44.2/100,000 women giving birth (95% CI: 39.4 - 49.5). The incidences in Australia and New Zealand were 47.4/100,000 (95% CI: 41.6- 54.0) and 36.0/100,000 (95% CI: 28.4-45.6) respectively. There were 12 perinatal deaths among the cases (perinatal death rate 38.7 per 1,000 births) and 10 among the controls (perinatal death rate 17.2 per 1,000 births). There were two maternal deaths among the cases, resulting in a case fatality rate of 0.7%. The causes of maternal death were cerebrovascular accident secondary to pulmonary embolism, and catastrophic postpartum haemorrhage due to placenta accreta. There were no maternal deaths among controls.

Almost half of the cases were first diagnosed by antenatal imaging (143, 48.5%), 132 (44.7%) were first diagnosed clinically at operation, and 16 (5.4%) were not diagnosed until histological confirmation following delivery; in four cases the time of diagnosis was not reported. In total, 184 (62%) cases were reported as being diagnosed at operation or by histology, and 107 cases reported as being diagnosed by antenatal imaging only (36%).

There were 213 (72.2%) cases with placenta accreta, 37 (12.5%) with placenta increta and 45 (15.3%) with placenta percreta, diagnosed by at least one of antenatal imaging, operation, or histology.

The median age of women with placenta accreta was 35 years (range 21-55) and the median BMI was 28kg/m2 (range 16.3-57.8) (Table 1). Over 80% of placenta accreta cases had a previous birth and 68% had a previous caesarean section. Eight percent of pregnancies among the cases were conceived following assisted reproductive technologies and 5% of the cases had current multiple pregnancies. Forty four percent of cases also had placenta praevia diagnosed prior to the birth (Table 1).

Women with placenta accreta were more likely to be older, have a higher BMI, a previous birth, previous caesarean section, placenta praevia diagnosed prior to delivery, current multiple pregnancy, and to have conceived following assisted reproductive technologies (Table 1).

Multivariate analysis was conducted separately for primiparous and multiparous women, as previous caesarean section is only applicable to women with a previous birth. In primiparous women, maternal age remained an independent risk factor for placenta accreta; mothers 40 or over had more than a 19-fold higher odds of placenta accreta compared to young mothers aged less than 30 (Table 2). The presence of a current multiple pregnancy was also a risk factor for placenta accreta in primiparous women (AOR: 6.1, 95% CI 1.1-34.1). In multiparous women, the independent risk factors were prior caesarean section (AOR ≥2 prior sections vs. 0: 13.8, 95% CI: 7.4-26.1) and current placenta praevia (AOR: 36.3, 95% CI: 14.0 – 93.7). Current placenta praevia was present in 50.2% of multiparous cases, compared to 10.8% of primiparous cases.

As the management of cases is expected to differ according to the knowledge of a placenta accreta, the cases were categorized by whether or not the placenta accreta was suspected prior to birth (Table 3). Of the cases, 169 (57.3%) had a placenta accreta suspected prior to birth. On average, women with a suspected placenta accreta had a more severe condition;

57 (33%) of suspected cases had a placenta increta or percreta, compared to 24 (19.5%) of non-suspected cases. Women with suspected placenta accreta were also more likely to have had a prior caesarean section (93%), than women with unsuspected placenta accreta (72%).

Cases were less likely to labour than controls (20% vs 79%); the majority of cases who labored had an unsuspected placenta accreta (Table 3). The one case with placenta accreta suspected prior to delivery that labored had a termination of pregnancy at 20 weeks. Additionally, cases were more likely to: give birth at an earlier gestation, to have a caesarean section, to be admitted to a high dependency unit (HDU) and to have a hysterectomy. Cases with a suspected placenta accreta were more likely to undergo hysterectomy than cases in which placenta accreta was not suspected prior to delivery (142/169; 84% vs 53/123; 43%), and both were more likely to undergo hysterectomy than controls (2/570; 0.4% underwent hysterectomy). In the two controls that required a hysterectomy, the underlying cause of hemorrhage was uterine atony. Of cases undergoing hysterectomy, 15 (7.7%) had no previous birth.

After adjusting for confounding factors, cases remained more likely to have a caesarean delivery (AOR: 4.6, 95% CI: 2.7 – 7.6), to be admitted to the intensive care unit (ICU)/HDU (AOR: 46.1, 95% CI: 22.3 – 95.4), and to have a hysterectomy (AOR: 209.0, 95% CI: 19.9 – 875.0). These analyses were adjusted for maternal age, BMI, smoking, number of previous caesarean sections, placenta praevia diagnosed prior to delivery, multiple pregnancy, and use of assisted reproductive technologies.

Babies born to mothers with placenta accreta were more likely to be preterm (median gestational age at birth 36 vs. 39 weeks), and have lower birthweights, with 40% vs. 9% of babies born weighing 2500g or less (Table 4). These babies were also more likely to have an Apgar score of 7 or less five minutes after birth, require resuscitation and to be admitted to a neonatal intensive care unit (NICU). Among cases, there was a higher chance of being discharged to another health facility and of neonatal death.

In the multivariate analysis, the following baby's outcomes remained significantly associated with placenta accreta: preterm birth (AOR: 5.0 95% CI: 3.2 – 7.8), low birthweight (AOR: 5.0, 95% CI: 2.9 – 8.4), admission to NICU (AOR: 4.4, 95% CI: 2.8 – 6.9), Apgar 5min <7 (AOR: 7.8, 95% CI: 3.1 – 19.9), resuscitation required (AOR: 4.5, 95% CI: 2.7 – 7.4) (Table 4). These analyses included singleton births only and were adjusted for maternal age, BMI, smoking, number of previous caesarean sections, placenta praevia diagnosed prior to delivery, and assisted reproductive technologies.

DISCUSSION

The incidence of placenta accreta identified in this study was 44.2/100,000 women giving birth. This is similar to the rates reported previously from single-centre studies in individual hospitals in New Zealand (60.2/100,000),[15] and Australia (38.8/100,000).[16] This paper is the first to report on the national incidence of placenta accreta in both Australia and New Zealand.

The rates of placenta accreta reported previously vary markedly, both across geographic populations and as a result of different definitions of 'placenta accreta'. The highest incidence has been reported in Israel at 900/100,000,[17] and a lower rate of 40/100,000 has been reported in the United States of America.[18] A review including 34 studies reported an average incidence of 189/100,000.[4] More recently the incidence of placenta accreta reported in the national United Kingdom Obstetric Surveillance System (UKOSS), was 17/100,000 women giving birth, from cases collected over a 12 month period in 2010-2011.[19] Both UKOSS and AMOSS are case-control studies that employed national active negative surveillance of cases. The UKOSS methods defined placenta accreta as "diagnosed histologically following hysterectomy or post-mortem or an abnormally adherent placenta, requiring active management, including conservative approaches where the placenta is left in situ" whereas the AMOSS study also included cases of diagnosis by antenatal imaging. It is possible that some cases included in this study were diagnosed at antenatal imaging and not found to have placenta accreta at the time of birth, which is not

uncommon.[3, 20] Of the 295 included cases, 107 (36%) were recorded as diagnosed by antenatal imaging only, with no recorded confirmation of placenta accrete at delivery. Reports on the accuracy of ultrasound to diagnose placenta accreta are variable, however antenatal imaging is generally considered to have a sensitivity of 77–100%, and specificity of 70–98%. [20-26] Further, 91/107 (85%) of these cases underwent hysterectomy following delivery, which suggests a confirmed diagnosis of placenta accreta, given that only 2/570; 0.4% of controls underwent hysterectomy. This provides some reassurance that included cases had clinical placenta accreta, although it remains a possibility that the cases may have included some women who did not have confirmed placenta accreta, and therefore this study may have overestimated the incidence of placenta accreta. It is also possible that the higher incidence of placenta accreta in Australasia as compared to the UK is a result of different exposure to risk factors. There appears to be a higher proportion of control women with risk factors for placenta accreta among the AMOSS cohort, for example rates of prior caesarean section (18% vs 15%), pregnancy conceived from assisted reproductive technologies (2.6% vs 1%), and maternal age of 35 or older (27% vs 24%).

This study reports four independent risk factors for placenta accreta: older maternal age, prior caesarean section, placenta praevia diagnosed prior to birth, and multiple birth; which have also been reported by other studies.[4, 27-29] Previous studies have also reported risk factors that this study did not find to be independent, specifically: smoking,[30] use of assisted reproductive technologies,[31] and sex of fetus.[32] Risk factors reported previously which were not measured in this study include hypertensive disorders, previous uterine surgery,[17, 33] previous intrauterine procedures such as dilation and curettage [34, 35], and elevated second-trimester serum levels of AFP and free β-hCG.[32]

Although the case definition establishes the outcome of this study as placenta accreta, it is important to consider the consequences of this condition for mother and baby. The maternal case fatality rate was 7/1000, with no maternal deaths among controls. The perinatal mortality rate was 39/1000 births for cases and 17/1000 births for controls. This is slightly

higher than reported previously in this population, and may be a result of the small numbers of deaths in this cohort (10/582), and the identification of controls as those delivering at the same hospital as cases, which are more likely to be tertiary hospitals.[9]

Maternal morbidity is high among women with placenta accreta. Just over one third of cases (35%) were admitted to the ICU or HDU, compared to less than 2% of controls. Two thirds of cases underwent a hysterectomy (66.4%) compared to only 0.4% of controls. Hysterectomy can be a devastating outcome for women wishing to expand their families, and is itself a significant operation. In this study, 42% of cases had an unsuspected placenta accreta and 43% of these had an unplanned hysterectomy. Of cases undergoing a hysterectomy, 92.3% had at least one baby previously, compared to 69% having had a prior birth among cases who did not undergo a hysterectomy. This likely reflects a higher incidence of placenta accreta in women with previous births and older maternal age, and may also be due to a stronger motivation to retain the uterus in women undergoing their first birth.

Women with placenta accreta were more likely to give birth earlier and consequently the babies born to these women were more often preterm, low birthweight, required resuscitation, admitted to NICU, and were more likely to die. Women with a suspected placenta accreta had a 74.7% preterm birth rate, which may reflect the management of suspected accreta with planned caesarean section; however the preterm birth rate was also much higher among those with an unsuspected placenta accreta compared to controls (37.6% vs 13.2%). Other studies have also reported higher preterm delivery rates and poorer outcomes for babies born to mothers with placenta accreta.[36] However, this study did not find a higher rate of small for gestational age babies among women with placenta accreta, which has been inconsistently reported in other studies.[4, 37]

Just over half of the cases included in this study had a placenta accreta suspected prior to delivery (169/295; 57.3%). This is similar to the rate of suspected placenta accreta reported in the UKOSS study of 50%.[19] It appears that women and babies with a suspected placenta accreta had inferior outcomes than those with an unknown placenta accreta, for

example higher rates of premature birth, hysterectomy, and admission to ICU/HDU. This possibly reflects the higher index of suspicion around more severe cases, for example one third of suspected cases were diagnosed with a more severe form of placenta accreta (increta or percreta) compared to 19.5% of unsuspected cases.

The major strength of the AMOSS study design is the active negative surveillance for cases. Cases were captured as they occurred which minimized the risk of recall bias compared to traditional case-control studies. Although the case ascertainment is believed to be high, it is not possible to be sure of the exact level of ascertainment achieved. The study audited clinical records and did not solely depend on administrative datasets which are often unreliable, particularly for uncommon conditions.

A possible limitation of this study relates to the possible inclusion of cases which were diagnosed antenatally, but which were not confirmed clinically at operation or on pathology; however this reflects diagnosis in real practice. Further, as it was not possible to assess how many of these cases were included, it was not possible to estimate the probability of misdiagnosis and consequent avoidable morbidity from unnecessary caesarean section. The inclusion criteria was women giving birth, defined as at least 400 g birthweight and/or at least 20 weeks' gestation. Therefore, any cases of accreta that resulted in an early second trimester miscarriage were not included; however the number of these cases is expected to be few. Additionally, denominator data for the number of births in Australian hospitals is an estimate because of the varying start time for hospitals in the study. A further limitation is that information was not collected on all possible risk factors, and therefore we were not able to assess these.

Future research could explore the role of antenatal diagnosis and screening of women with risk factors for placenta accreta. A significant proportion of the cases in this study had an unsuspected placenta accreta, and nearly half of these underwent an unplanned hysterectomy. This is despite routine ultrasound for assessment of the placenta at approximately 20 weeks' gestation in these countries.

This national study from Australia and New Zealand confirms the incidence of placenta accreta in this high income setting at approximately one in two thousand women giving birth. Although the condition remains rare, it is associated with a high risk of severe morbidity, and in a minority of cases, maternal death. The independent risk factors for placenta accreta in primiparous women were advanced maternal age and current multiple pregnancy. In multiparous women, previous caesarean birth and current placenta praevia were associated with an increased risk of placenta accreta. Further research on the role of antenatal diagnosis and screening in women with risk factors, particularly previous caesarean delivery, is warranted to inform clinical decision making about place and mode of birth, and to minimize risk of maternal and perinatal morbidity and mortality.

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CONTRIBUTION TO AUTHORSHIP

CF, MP, ES, CM, WP, DE, MK, CH conceptualized and designed the study protocol and case report forms. GV. ES managed data collection and oversaw operational aspects of the study. SL, ZL, ES, CF devised the data analysis. ZL, AW undertook the data analysis. CF, SL, ES and ZL led the drafting of the paper. All authors revised the manuscript and approved the final draft.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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DATA SHARING STATEMENT

No additional data are available.

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Table 1 Demographics and obstetric characteristics

	Case	Control	p-value
	N(%)	N(%)	
Total	295(100.0)	570(100.0)	
Country			
Australia	227(76.9)	436(76.5)	0.88
New Zealand	68(23.1)	134(23.5)	
Maternal age			
< 25	7(2.4)	93(16.3)	
25-29	44(14.9)	147(25.8)	
30-34	94(31.9)	177(31.1)	<0.001
35-39	112(38.0)	121(21.2)	
≥40	38(12.9)	32(5.6)	
Indigenous status (Australian only)			
Yes	11(4.8)	13(3.0)	0.21
No	202(89.0)	403(92.4)	
Not stated	14(6.2)	20(4.6)	
Ethnicity (New Zealand only)			
Maori	13(19.1)	18(13.4)	
New Zealand European	34(50.0)	63(47.0)	0.34
Pacific Peoples	5(7.4)	17(12.7)	
Other	12(17.6)	34(25.4)	
Not stated	4(5.9)	2(1.5)	
Body Mass Index (kg/m^2)			
<25	115(39.0)	272(47.7)	
25-29.9	66(22.4)	128(22.5)	<0.05
≥30	78(26.4)	112(19.6)	
Not stated	36(12.2)	58(10.2)	
Smoking during pregnancy			
Yes	56(19.0)	97(17.0)	0.45
No	215(72.9)	429(75.3)	
Not stated	24(8.1)	44(7.7)	
Parity			
0	46(15.6)	240(42.1)	
1-2	159(53.9)	274(48.1)	<0.001
≥3	90(30.5)	56(9.8)	
Number of previous caesarean deliveries			
No prior caesarean delivery	43(14.6)	225(39.5)	
1	89(30.2)	80(14.0)	
2	62(21.0)	19(3.3)	<0.001
≥3	50(16.9)	3(0.5)	
Not applicable (no prior births)	46(15.6)	240(42.1)	
Not stated	5(1.7)	3(0.5)	
Last pregnancy delivery by caesarean delivery			
Yes	188(63.7)	91(16.0)	<0.001

No	55(18.6)	234(41.1)	
Not applicable (no prior births)	46(15.6)	240(42.1)	
Not stated	6(2.0)	5(0.9)	
Placenta praevia during pregnancy			
Yes	130(44.1)	8(1.4)	<0.001
No	165(55.9)	562(98.6)	
Multiple pregnancy			
Yes	15(5.1)	13(2.3)	<0.05
No	280(94.9)	555(97.4)	
Not stated	0(0.0)	2(0.4)	
Assisted conception			
Yes	24(8.1)	15(2.6)	<0.001
No	259(87.8)	521(91.4)	
Not stated	12(4.1)	34(6.0)	

Table 2 Risk factor analysis including cases and controls

	Primiparous women		Multiparous women	
	OR (95% CI)	AOR (95% CI)*	OR (95% CI)	AOR (95% CI)†
Maternal age				
< 30	Ref	Ref	Ref	Ref
30-34	8.0(2.6-24.9)	6.3(2.0-20.0)	1.7(1.-,2.7)	1.7(0.9-3.2)
35-39	11.0(3.5-34.9)	7.0(2.1-23.6)	3.1(2.0-4.8)	2.7(1.4-5.2)
≥40	30.7(8.2-115.9)	19.1(4.6-80.3)	3.1(1.6-6.0)	2.0(0.8-5.0)
Body Mass Index (kg/m^2)				
<25	Ref	Ref	Ref	Ref
25-29.9	1.2(0.6-2.6)	1.4(0.6-3.2)	1.1(0.7-1.8)	0.8(0.4-1.4)
≥30	0.7(0.3-2.0)	0.7(0.2-2.2)	1.4(0.9-2.1)	0.8(0.5-1.4)
Smoking during pregnancy	0.2(0.1-1.0)	0.4(0.1-1.8)	1.3(0.9-2.0)	1.3(0.7-2.4)
Number of previous caesarean births				
No prior caesarean delivery	n.a	n.a	Ref	Ref
1	n.a	n.a	5.8(3.7-9.1)	3.7(2.2-6.3)
≥2	n.a	n.a	24.8(14.3-43.1)	13.8(7.4-26.1)
Placenta praevia during pregnancy	9.6(2.2-41.9)	3.0(0.6-15.2)	64.9(25.9-162.5)	36.3(14.0-93.7)
Multiple pregnancy	14.2(3.5-57.2)	6.1(1.1-34.1)	1.1(0.4-2.7)	1.5(0.5-4.9)
Assisted conception	5.4(2.2-13.1)	1.5(0.5-5.1)	4.4(1.4-13.7)	2.6(0.6-11.2)

*Adjusted for maternal age, body mass index, smoking, placenta praevia during pregnancy, multiple pregnancy, and assisted conception

†Adjusted for maternal age, body mass index, smoking, number of previous caesarean deliveries, placenta praevia during pregnancy, multiple pregnancy, and assisted conception

OR: odds ratio, AOR: adjusted odds ratio, Ref: reference value, n.a: not applicable

Cindy Farquhar

Table 3 Labour, birth and maternal morbidity among cases with suspected and unsuspected placenta accreta prior to delivery, and controls

	Case			Control (n=570)	p-value†
	PA suspected antenatally (n=169)	PA **not** suspected antenatally (n=123)	Total* (n=295)		
	N(%)	N(%)	N(%)	N(%)	
Did the woman labour					
Yes	7(4.1)	51(41.5)	59(20.0)	451(79.1)	<0.001
No	162(95.9)	72(58.5)	236(80.0)	117(20.5)	
Not stated	0(0.0)	0(0.0)	0(0.0)	2(0.4)	
Induced labour					
Yes	1(14.3)	16(31.4)	17(28.8)	116(25.7)	0.55
No	5(71.4)	34(66.7)	40(67.8)	329(72.9)	
Not stated	1(14.3)	1(2.0)	2(3.4)	6(1.3)	
Gestation at birth, weeks, median	35.0	38.0	36.0	39.0	<0.001
Method of birth					
Unassisted vaginal birth	1(0.6)	30(24.4)	31(10.5)	314(55.1)	<0.001
Instrumental vaginal birth	0(0.0)	5(4.1)	5(1.7)	71(12.5)	
Planned caesarean birth	140(82.8)	50(40.7)	190(64.4)	107(18.8)	
Unplanned caesarean birth	28(16.6)	38(30.9)	69(23.4)	77(13.5)	
Not stated	0(0.0)	0(0.0)	0(0.0)	1(0.2)	
Admission to ICU					
Yes	65(38.5)	40(32.5)	105(35.6)	6(1.1)	<0.001
No	104(61.5)	81(65.9)	188(63.7)	564(98.9)	
Not stated	0(0.0)	2(1.6)	2(0.7)	0(0.0)	
Admission to HDU					
Yes	68(40.2)	32(26.0)	101(34.2)	8(1.4)	<0.001
No	100(59.2)	89(72.4)	191(64.7)	562(98.6)	
Not stated	1(0.6)	2(1.6)	3(1.0)	0(0.0)	
Had hysterectomy					
Yes	142(84.0)	53(43.1)	196(66.4)	2(0.4)	<0.001
No	27(16.0)	69(56.1)	98(33.2)	568(99.6)	
Not stated	0(0.0)	1(0.8)	1(0.3)	0(0.0)	
Maternal death					
Yes	1(0.6)	1(0.8)	2(0.7)	0(0.0)	0.12
No	168(99.4)	122(99.2)	293(99.3)	570(100.0)	

PA: placenta accreta, ICU: intensive care unit; HDU: high dependency unit

* Includes 3 cases where it was not known whether PA was suspected prior to birth.

† Total number of cases vs control.

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Table 4 Perinatal outcomes among births born to women with suspected and unsuspected placenta accreta prior to delivery, and controls

	Case			Control (n= 582)	p-value†
	PA suspected antenatally (n= 174)	PA not suspected antenatally (n= 133)	Total* (n= 310)		
	N(%)	N(%)	N(%)	N(%)	
Fetal deaths	5(2.9)	4(3.0)	9(2.9)	5(0.9)	<0.05
Perinatal deaths	7(4.0)	5(3.8)	12(3.9)	10(1.7)	<0.05
Sex					
Male	87(50.0)	55(41.4)	142(45.8)	281(48.3)	0.53
Female	84(48.3)	78(58.6)	165(53.2)	299(51.4)	
Not stated	3(1.7)	0(0.0)	3(1.0)	2(0.3)	
Gestational age, weeks, median	35.0	38.0	36.0	39.0	<0.001
Preterm birth (<37 weeks)					
Yes	130(74.7)	50(37.6)	183(59.0)	77(13.2)	<0.001
No	43(24.7)	83(62.4)	126(40.6)	503(86.4)	
Not stated	1(0.6)	0(0.0)	1(0.3)	2(0.3)	
Birthweight*, g, mean	2468.3(±709.1)	2870.0(±847.8)	2640.3(±795.8)	3281.4(±615.8)	<0.001
Low birthweight *(<2500g)					
Yes	81(48.5)	38(29.5)	120(40.1)	54(9.4)	<0.001
No	85(50.9)	88(68.2)	175(58.5)	517(89.6)	
Not stated	1(0.6)	3(2.3)	4(1.3)	6(1.0)	
Small for gestational age*					
Yes	8(4.8)	14(10.9)	22(7.4)	55(9.5)	0.29
No	158(94.6)	112(86.8)	273(91.3)	516(89.4)	
Not stated	1(0.6)	3(2.3)	4(1.3)	6(1.0)	
Admission to NICU*					
Yes	130(77.8)	51(39.5)	183(61.2)	90(15.6)	<0.001
No	36(21.6)	76(58.9)	113(37.8)	479(83.0)	
Not stated	1(0.6)	2(1.6)	3(1.0)	8(1.4)	
Apgar score at 5 minutes*					
<7	59(35.3)	7(5.4)	66(22.1)	9(1.6)	<0.001
7-10	106(63.5)	120(93.0)	229(76.6)	559(96.9)	
Not stated	2(1.2)	2(1.6)	4(1.3)	9(1.6)	
Resuscitation*					
Yes	99(59.3)	29(22.5)	130(43.5)	49(8.5)	<0.001
No	65(38.9)	96(74.4)	162(54.2)	520(90.1)	
Not stated	3(1.8)	4(3.1)	7(2.3)	8(1.4)	
Separation status*					
Discharged home	119(71.3)	111(86.0)	232(77.6)	542(93.9)	
Transferred to another health facility/other	41(24.6)	16(12.4)	58(19.4)	28(4.9)	<0.001
Neonatal death	2(1.2)	1(0.8)	3(1.0)	5(0.9)	
Not stated	5(3.0)	1(0.8)	6(2.0)	2(0.3)	

*Live births only

†case vs control PA: placenta accreta, NICU: neonatal intensive care unit

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – line 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – see Abstract
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – - see Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses - see Introduction lines 100-104
Methods		
Study design	4	Present key elements of study design early in the paper – see start of Methods
Setting	5	Describe the setting (lines 110-114), locations (lines 110-114), and relevant dates including periods of recruitment (lines 115-116), exposure (lines 115-116), follow-up (lines 115-116), and data collection (lines 115-116)
Participants	6	(*a*) Give the eligibility criteria (lines 118-125), and the sources and methods of case ascertainment and control selection (lines 118-125). Give the rationale for the choice of cases and controls
		(*b*) For matched studies, give matching criteria and the number of controls per case NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable - see Methods and Results
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group - see Methods and Results
Bias	9	Describe any efforts to address potential sources of bias - see lines 291-306
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why - see lines 141-156
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding- see lines 141-156
		(*b*) Describe any methods used to examine subgroups and interactions - see lines 141-156
		(*c*) Explain how missing data were addressed - see lines 141-156
		(*d*) If applicable, explain how matching of cases and controls was addressed NA
		(*e*) Describe any sensitivity analyses NA
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed - see lines 158-161
		(b) Give reasons for non-participation at each stage NA
		(c) Consider use of a flow diagram NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – Table 1
		(b) Indicate number of participants with missing data for each variable of interest

Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure – Tables
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – all through Results
		(*b*) Report category boundaries when continuous variables were categorized – See Tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – See Tables and Results
Discussion		
Key results	18	Summarise key results with reference to study objectives – first half of Comment section
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – see lines 291-306
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results – start of Comment
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - reported

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Incidence, risk factors, and perinatal outcomes for placenta accreta in Australia and New Zealand: A case-control study

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Title: Incidence, risk factors, and perinatal outcomes for placenta accreta in Australia and New Zealand: A case-control study

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ABSTRACT

Objective Estimate the incidence of placenta accreta and describe risk factors, clinical practice and perinatal outcomes.

Design Case-control study.

Setting Sites in Australia and New Zealand with at least 50 births per year

Participants Cases were women giving birth (≥20 weeks or fetus ≥400g) who were diagnosed with placenta accreta by antenatal imaging, at operation, or by pathology specimens between 2010-2012. Controls were two births immediately prior to a case. A total of 295 cases were included and 570 controls.

Methods Data were collected using the Australasian Maternity Outcomes Surveillance System.

Primary and secondary outcome measures: Incidence, risk factors (e.g. prior caesarean section (CS), maternal age) and clinical outcomes of placenta accreta (e.g. CS, hysterectomy, and death).

Results The incidence of placenta accreta was 44.2/100,000 women giving birth (95% CI: 39.4 - 49.5), however this may overestimated due to the case definition used. In primiparous women, an increased odds of placenta accreta was observed in older women (AOR women ≥40 vs. <30: 19.1, 95% CI: 4.6-80.3), and current multiple birth (AOR: 6.1, 95% CI 1.1-34.1). In multiparous women, independent risk factors were prior CS (AOR ≥2 prior sections vs. 0: 13.8, 95% CI: 7.4-26.1), and current placenta praevia (AOR: 36.3, 95% CI: 14.0 – 93.7). There were 2 maternal deaths (case fatality rate 0.7%).

Women with placenta accreta were more likely to have a caesarean section (AOR: 4.6, 95% CI: 2.7 – 7.6), to be admitted to the ICU/HDU (AOR: 46.1, 95% CI: 22.3 – 95.4), and to have a hysterectomy (AOR: 209.0, 95% CI: 19.9 – 875.0). Babies born to women with placenta accreta were more likely to be preterm, be admitted to NICU, and require resuscitation.

Conclusions Placenta accreta is associated with a high risk of severe morbidity, peripartum hysterectomy and in a minority of cases, maternal death.

Key words: caesarean, c-section, placenta accreta, placentation

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first national and bi-national case-control study of placenta accreta in Australia and New Zealand
- This case control study used active surveillance of cases by dedicated researchers, limiting recall bias and errors common in administrative datasets
- This study may have included cases which were diagnosed antenatally, but which were not confirmed clinically at operation or on pathology and therefore not true cases of placenta accreta
- Denominator data for the number of births in Australian hospitals is an estimate because of the varying start time for hospitals in the study.

INTRODUCTION

Placenta accreta is an uncommon condition occurring during pregnancy which is characterized by abnormal placentation. The severity of abnormal placentation can be classified into three grades based on histopathology: the least severe and most common presentation is placenta accreta, in which the placental villi penetrate only to the surface of the myometrium. Placenta increta is characterized by invasion of placental villi into the myometrium. The most severe form is placenta percreta, characterized by invasion of villi beyond the myometrium to the uterine serosa, and in some cases involving adjacent organs such as the bladder.[1] The term 'placenta accreta' refers to all three conditions in this paper. Placenta accreta is associated with major pregnancy complications such as massive blood loss and hysterectomy, and is potentially life-threatening. Once the diagnosis of placenta accreta is established, the decision about mode of birth requires multidisciplinary team planning, and often involves complex surgery or radiological interventions to reduce maternal and neonatal morbidity.[2, 3]

The incidence of placenta accreta is believed to be increasing globally.[2, 3] This is likely attributable to an increase in caesarean sections and trends towards older women giving birth, both of which are independent risk factors for placenta accreta.[4, 5] There are a growing number of caesarean sections in Australia and New Zealand,[6] however the epidemiology and clinical practices for managing placenta accreta in these countries has not been previously reported. The prevalence of risk-factors for this condition may be different in the Australian and New Zealand population, such as the prevalence of previous caesarian births. A case-control study with active surveillance was undertaken with the aim of estimating the incidence of placenta accreta in Australia and New Zealand, and describing risk factors, clinical practices and outcomes, for women affected by this condition and their babies.

MATERIALS AND METHODS

A bi-national population-based case-control study was undertaken using the research platform of the Australasian Maternity Outcomes Surveillance System (AMOSS). AMOSS was established across maternity units in Australia and New Zealand in 2009 to study rare and serious disorders of pregnancy.[7, 8] There were six studies conducted contemporaneously including studies on: amniotic fluid embolism, antenatal pulmonary embolism, eclampsia, super-obesity and peripartum hysterectomy, which used a similar study design and data collection methodology. Data were collected from participating sites, which were public and private maternity units with more than 50 births per year in Australia and New Zealand, incorporating all service levels. Australian sites (n = 269) progressively joined AMOSS on completion of relevant ethics and governance approvals. In New Zealand, all 24 maternity units participated (100% of hospital births).[8]

Women were identified by AMOSS-participating sites from January 2010 to December 2011 (Australia), and to December 2012 (New Zealand). All AMOSS hospital-based data collectors received study information on the surveillance period, recruitment, case definition, and inclusion and exclusion criteria. Central support was available for local data collectors, including confirmation that individual cases satisfied the inclusion criteria. Nominated clinicians and midwives were contacted each month using an active surveillance system, querying whether a case had occurred that month. Data collectors identified cases through multiple sources: review of routine data collection within the hospital, audit committees, clinician notification and request to clinicians of potential cases. The average monthly response rate was 91%.

Cases were defined as: women giving birth who were diagnosed with placenta accreta by either antenatal imaging, at operation or by pathology specimens. The type of diagnosis was re-coded according to the earliest diagnosis. For example, a case diagnosed both by antenatal imaging and by pathology specimen was coded as diagnosed by antenatal imaging. Giving birth was defined as the birth of one or more live or stillborn infants of at

least 400 g birthweight and/or at least 20 weeks' gestation.[9, 10] The two women giving birth immediately prior to the case in the same hospital were selected as controls. Perinatal deaths included fetal deaths of at least 400 g birthweight or 20 weeks' gestation, and neonatal deaths occurring within 28 days after birth.

Data were collected using secure, web-based forms which captured general demographic and pregnancy data, and case-specific information about prior obstetric history, current pregnancy, and placenta accreta diagnosis and clinical practice, such as use of hysterectomy. For controls, the outcome of hysterectomy was obtained from a free-text field on maternal morbidity, and by probabilistic matching against the AMOSS hysterectomy cohort.

Data collectors at participating hospitals were contacted regarding missing data or where data were not consistent with expected values. Logic checks were run on the data to identify any impossible or improbable scenarios. Free text responses to questions regarding medical or obstetric morbidity were classified according to ICD-10-Australian Modification. All data were collected in a non-identifiable manner.

Ethics approval for AMOSS was granted by the NSW Population and Health Services Research Ethics Committee and multiple Human Research Ethics Committees across Australia and the multiregional ethics approval (MEC/09/73/EXP) in New Zealand.[11]

After adjusting for the phased implementation of AMOSS, there were an estimated 478,820 women giving birth (486,003 babies born) in Australia and 189,116 (190,408 babies born) in New Zealand across the participating maternity sites during the study period. In New Zealand these denominators were calculated from the Ministry of Health data, [12-14] and in Australia by using the number of days' participation in the study multiplied by number of births per day for that hospital, which gave approximate coverage ranging from 75% in 2010 to 82% in 2011 of all women giving birth in Australia, respectively. Incidence rates were calculated with 95% confidence intervals (CI). Fisher's exact test, Chi-square test, independent samples t-test and Mann–Whitney U-test were used to investigate differences in demographics and obstetric characteristics, maternal and perinatal outcomes between

cases and the controls. Multivariate logistic regression was used to examine the risk factors for placenta accreta by parity, and to compare the maternal and perinatal outcomes of cases and controls. Odds ratio (OR), adjusted odds ratio (AOR) and 95% CI were calculated. Adjustment was made for maternal age, body mass index (BMI), smoking status during pregnancy, parity, number of previous caesarean births, placenta praevia during pregnancy, multiple pregnancies, and assisted reproductive technologies. Data were analysed using the Statistical Package for the Social Sciences software, version 22.0 (IBM Corporation, Somers, NY, USA).

RESULTS

Of the 308 cases notified to AMOSS, 295 were eligible after excluding 13 cases; seven outside the study period, three duplicate notifications, and three not satisfying the birth definition. Of the 295 cases, 227 women were from Australia and 68 from New Zealand. Data were available for 570 controls, as the data for 20 controls was missing.

The incidence of placenta accreta for the study period was 44.2/100,000 women giving birth (95% CI: 39.4 - 49.5). The incidences in Australia and New Zealand were 47.4/100,000 (95% CI: 41.6- 54.0) and 36.0/100,000 (95% CI: 28.4-45.6) respectively. There were 12 perinatal deaths among the cases (perinatal death rate 38.7 per 1,000 births) and 10 among the controls (perinatal death rate 17.2 per 1,000 births). There were two maternal deaths among the cases, resulting in a case fatality rate of 0.7%. The causes of maternal death were cerebrovascular accident secondary to pulmonary embolism, and catastrophic postpartum haemorrhage due to placenta accreta. There were no maternal deaths among controls.

Almost half of the cases were first diagnosed by antenatal imaging (143, 48.5%), 132 (44.7%) were first diagnosed clinically at operation, and 16 (5.4%) were not diagnosed until histological confirmation following delivery; in four cases the time of diagnosis was not reported. In total, 184 (62%) cases were reported as being diagnosed at operation or by histology, and 107 cases reported as being diagnosed by antenatal imaging only (36%).

There were 213 (72.2%) cases with placenta accreta, 37 (12.5%) with placenta increta and 45 (15.3%) with placenta percreta, diagnosed by at least one of antenatal imaging, operation, or histology.

The median age of women with placenta accreta was 35 years (range 21-55) and the median BMI was 28kg/m2 (range 16.3-57.8) (Table 1). Over 80% of placenta accreta cases had a previous birth and 68% had a previous caesarean section. Eight percent of pregnancies among the cases were conceived following assisted reproductive technologies and 5% of the cases had current multiple pregnancies. Forty four percent of cases also had placenta praevia diagnosed prior to the birth (Table 1).

Women with placenta accreta were more likely to be older, have a higher BMI, a previous birth, previous caesarean section, placenta praevia diagnosed prior to delivery, current multiple pregnancy, and to have conceived following assisted reproductive technologies (Table 1).

Multivariate analysis was conducted separately for primiparous and multiparous women, as previous caesarean section is only applicable to women with a previous birth. In primiparous women, maternal age remained an independent risk factor for placenta accreta; mothers 40 or over had more than a 19-fold higher odds of placenta accreta compared to young mothers aged less than 30 (Table 2). The presence of a current multiple pregnancy was also a risk factor for placenta accreta in primiparous women (AOR: 6.1, 95% CI 1.1-34.1). In multiparous women, the independent risk factors were prior caesarean section (AOR ≥2 prior sections vs. 0: 13.8, 95% CI: 7.4-26.1) and current placenta praevia (AOR: 36.3, 95% CI: 14.0 – 93.7). Current placenta praevia was present in 50.2% of multiparous cases, compared to 10.8% of primiparous cases.

As the management of cases is expected to differ according to the knowledge of a placenta accreta, the cases were categorized by whether or not the placenta accreta was suspected prior to birth (Table 3). Of the cases, 169 (57.3%) had a placenta accreta suspected prior to birth. On average, women with a suspected placenta accreta had a more severe condition;

57 (33%) of suspected cases had a placenta increta or percreta, compared to 24 (19.5%) of non-suspected cases. Women with suspected placenta accreta were also more likely to have had a prior caesarean section (93%), than women with unsuspected placenta accreta (72%).

Cases were less likely to labour than controls (20% vs 79%); the majority of cases who labored had an unsuspected placenta accreta (Table 3). The one case with placenta accreta suspected prior to delivery that labored had a termination of pregnancy at 20 weeks. Additionally, cases were more likely to: give birth at an earlier gestation, to have a caesarean section, to be admitted to a high dependency unit (HDU) and to have a hysterectomy. Cases with a suspected placenta accreta were more likely to undergo hysterectomy than cases in which placenta accreta was not suspected prior to delivery (142/169; 84% vs 53/123; 43%), and both were more likely to undergo hysterectomy than controls (2/570; 0.4% underwent hysterectomy). In the two controls that required a hysterectomy, the underlying cause of hemorrhage was uterine atony. Of cases undergoing hysterectomy, 15 (7.7%) had no previous birth.

After adjusting for confounding factors, cases remained more likely to have a caesarean delivery (AOR: 4.6, 95% CI: 2.7 – 7.6), to be admitted to the intensive care unit (ICU)/HDU (AOR: 46.1, 95% CI: 22.3 – 95.4), and to have a hysterectomy (AOR: 209.0, 95% CI: 19.9 – 875.0). These analyses were adjusted for maternal age, BMI, smoking, number of previous caesarean sections, placenta praevia diagnosed prior to delivery, multiple pregnancy, and use of assisted reproductive technologies.

Babies born to mothers with placenta accreta were more likely to be preterm (median gestational age at birth 36 vs. 39 weeks), and have lower birthweights, with 40% vs. 9% of babies born weighing 2500g or less (Table 4). These babies were also more likely to have an Apgar score of 7 or less five minutes after birth, require resuscitation and to be admitted to a neonatal intensive care unit (NICU). Among cases, there was a higher chance of being discharged to another health facility and of neonatal death.

In the multivariate analysis, the following baby's outcomes remained significantly associated with placenta accreta: preterm birth (AOR: 5.0 95% CI: 3.2 – 7.8), low birthweight (AOR: 5.0, 95% CI: 2.9 – 8.4), admission to NICU (AOR: 4.4, 95% CI: 2.8 – 6.9), Apgar 5min <7 (AOR: 7.8, 95% CI: 3.1 – 19.9), resuscitation required (AOR: 4.5, 95% CI: 2.7 – 7.4) (Table 4). These analyses included singleton births only and were adjusted for maternal age, BMI, smoking, number of previous caesarean sections, placenta praevia diagnosed prior to delivery, and assisted reproductive technologies.

DISCUSSION

The incidence of placenta accreta identified in this study was 44.2/100,000 women giving birth. This is similar to the rates reported previously from single-centre studies in individual hospitals in New Zealand (60.2/100,000),[15] and Australia (38.8/100,000).[16] This paper is the first to report on the national incidence of placenta accreta in both Australia and New Zealand.

The rates of placenta accreta reported previously vary markedly, both across geographic populations and as a result of different definitions of 'placenta accreta'. The highest incidence has been reported in Israel at 900/100,000,[17] and a lower rate of 40/100,000 has been reported in the United States of America.[18] A review including 34 studies reported an average incidence of 189/100,000.[4] More recently the incidence of placenta accreta reported in the national United Kingdom Obstetric Surveillance System (UKOSS), was 17/100,000 women giving birth, from cases collected over a 12 month period in 2010-2011.[19] Both UKOSS and AMOSS are case-control studies that employed national active surveillance of cases. The UKOSS methods defined placenta accreta as "diagnosed histologically following hysterectomy or post-mortem or an abnormally adherent placenta, requiring active management, including conservative approaches where the placenta is left in situ" whereas the AMOSS study also included cases of diagnosis by antenatal imaging. It is possible that some cases included in this study were diagnosed at antenatal imaging and not found to have placenta accreta at the time of birth, which is not uncommon.[3, 20] Of the

295 included cases, 107 (36%) were recorded as diagnosed by antenatal imaging only, with no recorded confirmation of placenta accrete at delivery. Reports on the accuracy of ultrasound to diagnose placenta accreta are variable, however antenatal imaging is generally considered to have a sensitivity of 77–100%, and specificity of 70–98%. [20-26] Further, 91/107 (85%) of these cases underwent hysterectomy following delivery, which suggests a confirmed diagnosis of placenta accreta, given that only 2/570; 0.4% of controls underwent hysterectomy. This provides some reassurance that included cases had clinical placenta accreta, although it remains a possibility that the cases may have included some women who did not have confirmed placenta accreta, and therefore this study may have overestimated the incidence of placenta accreta. It is also possible that the higher incidence of placenta accreta in Australasia as compared to the UK is a result of different exposure to risk factors. There appears to be a higher proportion of control women with risk factors for placenta accreta among the AMOSS cohort, for example rates of prior caesarean section (18% vs 15%), pregnancy conceived from assisted reproductive technologies (2.6% vs 1%), and maternal age of 35 or older (27% vs 24%).

This study reports four independent risk factors for placenta accreta: older maternal age, prior caesarean section, placenta praevia diagnosed prior to birth, and multiple birth; which have also been reported by other studies.[4, 27-29] Previous studies have also reported risk factors that this study did not find to be independent, specifically: smoking,[30] use of assisted reproductive technologies,[31] and sex of fetus.[32] Risk factors reported previously which were not measured in this study include hypertensive disorders, previous uterine surgery,[17, 33] previous intrauterine procedures such as dilation and curettage [34, 35], and elevated second-trimester serum levels of AFP and free β-hCG.[32]

Although the case definition establishes the outcome of this study as placenta accreta, it is important to consider the consequences of this condition for mother and baby. The maternal case fatality rate was 7/1000, with no maternal deaths among controls. The perinatal mortality rate was 39/1000 births for cases and 17/1000 births for controls. This is slightly

higher than reported previously in this population, and may be a result of the small numbers of deaths in this cohort (10/582), and the identification of controls as those delivering at the same hospital as cases, which are more likely to be tertiary hospitals.[9]

Maternal morbidity is high among women with placenta accreta. Just over one third of cases (35%) were admitted to the ICU or HDU, compared to less than 2% of controls. Two thirds of cases underwent a hysterectomy (66.4%) compared to only 0.4% of controls. Hysterectomy can be a devastating outcome for women wishing to expand their families, and is itself a significant operation. In this study, 42% of cases had an unsuspected placenta accreta and 43% of these had an unplanned hysterectomy. Of cases undergoing a hysterectomy, 92.3% had at least one baby previously, compared to 69% having had a prior birth among cases who did not undergo a hysterectomy. This likely reflects a higher incidence of placenta accreta in women with previous births and older maternal age, and may also be due to a stronger motivation to retain the uterus in women undergoing their first birth.

Women with placenta accreta were more likely to give birth earlier and consequently the babies born to these women were more often preterm, low birthweight, required resuscitation, admitted to NICU, and were more likely to die. Women with a suspected placenta accreta had a 74.7% preterm birth rate, which may reflect the management of suspected accreta with planned caesarean section; however the preterm birth rate was also much higher among those with an unsuspected placenta accreta compared to controls (37.6% vs 13.2%). Other studies have also reported higher preterm delivery rates and poorer outcomes for babies born to mothers with placenta accreta.[36] However, this study did not find a higher rate of small for gestational age babies among women with placenta accreta, which has been inconsistently reported in other studies.[4, 37]

Just over half of the cases included in this study had a placenta accreta suspected prior to delivery (169/295; 57.3%). This is similar to the rate of suspected placenta accreta reported in the UKOSS study of 50%.[19] It appears that women and babies with a suspected placenta accreta had inferior outcomes than those with an unknown placenta accreta, for

example higher rates of premature birth, hysterectomy, and admission to ICU/HDU. This possibly reflects the higher index of suspicion around more severe cases, for example one third of suspected cases were diagnosed with a more severe form of placenta accreta (increta or percreta) compared to 19.5% of unsuspected cases.

The major strength of the AMOSS study design is the active surveillance for cases. Cases were captured as they occurred which minimized the risk of recall bias compared to traditional case-control studies. Although the case ascertainment is believed to be high, it is not possible to be sure of the exact level of ascertainment achieved. The study audited clinical records and did not solely depend on administrative datasets which are often unreliable, particularly for uncommon conditions.

A possible limitation of this study relates to the possible inclusion of cases which were diagnosed antenatally, but which were not confirmed clinically at operation or on pathology; however this reflects diagnosis in real practice. Further, as it was not possible to assess how many of these cases were included, it was not possible to estimate the probability of misdiagnosis and consequent avoidable morbidity from unnecessary caesarean section. The inclusion criteria was women giving birth, defined as at least 400 g birthweight and/or at least 20 weeks' gestation. Therefore, any cases of accreta that resulted in an early second trimester miscarriage were not included; however the number of these cases is expected to be few. Additionally, denominator data for the number of births in Australian hospitals is an estimate because of the varying start time for hospitals in the study. A further limitation is that information was not collected on all possible risk factors, and therefore we were not able to assess these.

Future research could explore the role of antenatal diagnosis and screening of women with risk factors for placenta accreta. A significant proportion of the cases in this study had an unsuspected placenta accreta, and nearly half of these underwent an unplanned hysterectomy. This is despite routine ultrasound for assessment of the placenta at approximately 20 weeks' gestation in these countries.

This national study from Australia and New Zealand confirms the incidence of placenta accreta in this high income setting at approximately one in two thousand women giving birth. Although the condition remains rare, it is associated with a high risk of severe morbidity, and in a minority of cases, maternal death. The independent risk factors for placenta accreta in primiparous women were advanced maternal age and current multiple pregnancy. In multiparous women, previous caesarean birth and current placenta praevia were associated with an increased risk of placenta accreta. Further research on the role of antenatal diagnosis and screening in women with risk factors, particularly previous caesarean delivery, is warranted to inform clinical decision making about place and mode of birth, and to minimize risk of maternal and perinatal morbidity and mortality.

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CONTRIBUTION TO AUTHORSHIP

CF, MP, ES, CM, WP, DE, MK, CH conceptualized and designed the study protocol and case report forms. GV. ES managed data collection and oversaw operational aspects of the study. SL, ZL, ES, CF devised the data analysis. ZL, AW undertook the data analysis. CF, SL, ES and ZL led the drafting of the paper. All authors revised the manuscript and approved the final draft.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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DATA SHARING STATEMENT

No additional data are available.

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Table 1 Demographics and obstetric characteristics

	Case	Control	p-value
	N(%)	N(%)	
Total	295(100.0)	570(100.0)	
Country			
Australia	227(76.9)	436(76.5)	0.88
New Zealand	68(23.1)	134(23.5)	
Maternal age			
< 25	7(2.4)	93(16.3)	
25-29	44(14.9)	147(25.8)	
30-34	94(31.9)	177(31.1)	<0.001
35-39	112(38.0)	121(21.2)	
≥40	38(12.9)	32(5.6)	
Indigenous status (Australian only)			
Yes	11(4.8)	13(3.0)	0.21
No	202(89.0)	403(92.4)	
Not stated	14(6.2)	20(4.6)	
Ethnicity (New Zealand only)			
Maori	13(19.1)	18(13.4)	
New Zealand European	34(50.0)	63(47.0)	0.34
Pacific Peoples	5(7.4)	17(12.7)	
Other	12(17.6)	34(25.4)	
Not stated	4(5.9)	2(1.5)	
Body Mass Index (kg/m^2)			
<25	115(39.0)	272(47.7)	
25-29.9	66(22.4)	128(22.5)	<0.05
≥30	78(26.4)	112(19.6)	
Not stated	36(12.2)	58(10.2)	
Smoking during pregnancy			
Yes	56(19.0)	97(17.0)	0.45
No	215(72.9)	429(75.3)	
Not stated	24(8.1)	44(7.7)	
Parity			
0	46(15.6)	240(42.1)	
1-2	159(53.9)	274(48.1)	<0.001
≥3	90(30.5)	56(9.8)	
Number of previous caesarean deliveries			
No prior caesarean delivery	43(14.6)	225(39.5)	
1	89(30.2)	80(14.0)	
2	62(21.0)	19(3.3)	<0.001
≥3	50(16.9)	3(0.5)	
Not applicable (no prior births)	46(15.6)	240(42.1)	
Not stated	5(1.7)	3(0.5)	
Last pregnancy delivery by caesarean delivery			
Yes	188(63.7)	91(16.0)	<0.001

No	55(18.6)	234(41.1)	
Not applicable (no prior births)	46(15.6)	240(42.1)	
Not stated	6(2.0)	5(0.9)	
Placenta praevia during pregnancy			
Yes	130(44.1)	8(1.4)	<0.001
No	165(55.9)	562(98.6)	
Multiple pregnancy			
Yes	15(5.1)	13(2.3)	<0.05
No	280(94.9)	555(97.4)	
Not stated	0(0.0)	2(0.4)	
Assisted conception			
Yes	24(8.1)	15(2.6)	<0.001
No	259(87.8)	521(91.4)	
Not stated	12(4.1)	34(6.0)	

Table 2 Risk factor analysis including cases and controls

	Primiparous women		Multiparous women	
	OR (95% CI)	AOR (95% CI)*	OR (95% CI)	AOR (95% CI)†
Maternal age				
< 30	Ref	Ref	Ref	Ref
30-34	8.0(2.6-24.9)	6.3(2.0-20.0)	1.7(1.-,2.7)	1.7(0.9-3.2)
35-39	11.0(3.5-34.9)	7.0(2.1-23.6)	3.1(2.0-4.8)	2.7(1.4-5.2)
≥40	30.7(8.2-115.9)	19.1(4.6-80.3)	3.1(1.6-6.0)	2.0(0.8-5.0)
Body Mass Index (kg/m^2)				
<25	Ref	Ref	Ref	Ref
25-29.9	1.2(0.6-2.6)	1.4(0.6-3.2)	1.1(0.7-1.8)	0.8(0.4-1.4)
≥30	0.7(0.3-2.0)	0.7(0.2-2.2)	1.4(0.9-2.1)	0.8(0.5-1.4)
Smoking during pregnancy	0.2(0.1-1.0)	0.4(0.1-1.8)	1.3(0.9-2.0)	1.3(0.7-2.4)
Number of previous caesarean births				
No prior caesarean delivery	n.a	n.a	Ref	Ref
1	n.a	n.a	5.8(3.7-9.1)	3.7(2.2-6.3)
≥2	n.a	n.a	24.8(14.3-43.1)	13.8(7.4-26.1)
Placenta praevia during pregnancy	9.6(2.2-41.9)	3.0(0.6-15.2)	64.9(25.9-162.5)	36.3(14.0-93.7)
Multiple pregnancy	14.2(3.5-57.2)	6.1(1.1-34.1)	1.1(0.4-2.7)	1.5(0.5-4.9)
Assisted conception	5.4(2.2-13.1)	1.5(0.5-5.1)	4.4(1.4-13.7)	2.6(0.6-11.2)

*Adjusted for maternal age, body mass index, smoking, placenta praevia during pregnancy, multiple pregnancy, and assisted conception

†Adjusted for maternal age, body mass index, smoking, number of previous caesarean deliveries, placenta praevia during pregnancy, multiple pregnancy, and assisted conception

OR: odds ratio, AOR: adjusted odds ratio, Ref: reference value, n.a: not applicable

Cindy Farquhar

Table 3 Labour, birth and maternal morbidity among cases with suspected and unsuspected placenta accreta prior to delivery, and controls

	Case			Control (n=570)	p-value†
	PA suspected antenatally (n=169)	PA **not** suspected antenatally (n=123)	Total* (n=295)		
	N(%)	N(%)	N(%)	N(%)	
Did the woman labour					
Yes	7(4.1)	51(41.5)	59(20.0)	451(79.1)	<0.001
No	162(95.9)	72(58.5)	236(80.0)	117(20.5)	
Not stated	0(0.0)	0(0.0)	0(0.0)	2(0.4)	
Induced labour					
Yes	1(14.3)	16(31.4)	17(28.8)	116(25.7)	0.55
No	5(71.4)	34(66.7)	40(67.8)	329(72.9)	
Not stated	1(14.3)	1(2.0)	2(3.4)	6(1.3)	
Gestation at birth, weeks, median	35.0	38.0	36.0	39.0	<0.001
Method of birth					
Unassisted vaginal birth	1(0.6)	30(24.4)	31(10.5)	314(55.1)	<0.001
Instrumental vaginal birth	0(0.0)	5(4.1)	5(1.7)	71(12.5)	
Planned caesarean birth	140(82.8)	50(40.7)	190(64.4)	107(18.8)	
Unplanned caesarean birth	28(16.6)	38(30.9)	69(23.4)	77(13.5)	
Not stated	0(0.0)	0(0.0)	0(0.0)	1(0.2)	
Admission to ICU					
Yes	65(38.5)	40(32.5)	105(35.6)	6(1.1)	<0.001
No	104(61.5)	81(65.9)	188(63.7)	564(98.9)	
Not stated	0(0.0)	2(1.6)	2(0.7)	0(0.0)	
Admission to HDU					
Yes	68(40.2)	32(26.0)	101(34.2)	8(1.4)	<0.001
No	100(59.2)	89(72.4)	191(64.7)	562(98.6)	
Not stated	1(0.6)	2(1.6)	3(1.0)	0(0.0)	
Had hysterectomy					
Yes	142(84.0)	53(43.1)	196(66.4)	2(0.4)	<0.001
No	27(16.0)	69(56.1)	98(33.2)	568(99.6)	
Not stated	0(0.0)	1(0.8)	1(0.3)	0(0.0)	
Maternal death					
Yes	1(0.6)	1(0.8)	2(0.7)	0(0.0)	0.12
No	168(99.4)	122(99.2)	293(99.3)	570(100.0)	

PA: placenta accreta, ICU: intensive care unit; HDU: high dependency unit

* Includes 3 cases where it was not known whether PA was suspected prior to birth.

† Total number of cases vs control.

Cindy Farquhar

Table 4 Perinatal outcomes among births born to women with suspected and unsuspected placenta accreta prior to delivery, and controls

	Case			Control (n= 582)	p-value†
	PA suspected antenatally (n= 174)	PA not suspected antenatally (n= 133)	Total* (n= 310)		
	N(%)	N(%)	N(%)	N(%)	
Fetal deaths	5(2.9)	4(3.0)	9(2.9)	5(0.9)	<0.05
Perinatal deaths	7(4.0)	5(3.8)	12(3.9)	10(1.7)	<0.05
Sex					
Male	87(50.0)	55(41.4)	142(45.8)	281(48.3)	0.53
Female	84(48.3)	78(58.6)	165(53.2)	299(51.4)	
Not stated	3(1.7)	0(0.0)	3(1.0)	2(0.3)	
Gestational age, weeks, median	35.0	38.0	36.0	39.0	<0.001
Preterm birth (<37 weeks)					
Yes	130(74.7)	50(37.6)	183(59.0)	77(13.2)	<0.001
No	43(24.7)	83(62.4)	126(40.6)	503(86.4)	
Not stated	1(0.6)	0(0.0)	1(0.3)	2(0.3)	
Birthweight*, g, mean	2468.3(±709.1)	2870.0(±847.8)	2640.3(±795.8)	3281.4(±615.8)	<0.001
Low birthweight *(<2500g)					
Yes	81(48.5)	38(29.5)	120(40.1)	54(9.4)	<0.001
No	85(50.9)	88(68.2)	175(58.5)	517(89.6)	
Not stated	1(0.6)	3(2.3)	4(1.3)	6(1.0)	
Small for gestational age*					
Yes	8(4.8)	14(10.9)	22(7.4)	55(9.5)	0.29
No	158(94.6)	112(86.8)	273(91.3)	516(89.4)	
Not stated	1(0.6)	3(2.3)	4(1.3)	6(1.0)	
Admission to NICU*					
Yes	130(77.8)	51(39.5)	183(61.2)	90(15.6)	<0.001
No	36(21.6)	76(58.9)	113(37.8)	479(83.0)	
Not stated	1(0.6)	2(1.6)	3(1.0)	8(1.4)	
Apgar score at 5 minutes*					
<7	59(35.3)	7(5.4)	66(22.1)	9(1.6)	<0.001
7-10	106(63.5)	120(93.0)	229(76.6)	559(96.9)	
Not stated	2(1.2)	2(1.6)	4(1.3)	9(1.6)	
Resuscitation*					
Yes	99(59.3)	29(22.5)	130(43.5)	49(8.5)	<0.001
No	65(38.9)	96(74.4)	162(54.2)	520(90.1)	
Not stated	3(1.8)	4(3.1)	7(2.3)	8(1.4)	
Separation status*					
Discharged home	119(71.3)	111(86.0)	232(77.6)	542(93.9)	
Transferred to another health facility/other	41(24.6)	16(12.4)	58(19.4)	28(4.9)	<0.001
Neonatal death	2(1.2)	1(0.8)	3(1.0)	5(0.9)	
Not stated	5(3.0)	1(0.8)	6(2.0)	2(0.3)	

*Live births only

†case vs control PA: placenta accreta, NICU: neonatal intensive care unit

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – line 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – see Abstract
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – - see Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses - see Introduction lines 100-104
Methods		
Study design	4	Present key elements of study design early in the paper – see start of Methods
Setting	5	Describe the setting (lines 110-114), locations (lines 110-114), and relevant dates including periods of recruitment (lines 115-116), exposure (lines 115-116), follow-up (lines 115-116), and data collection (lines 115-116)
Participants	6	(*a*) Give the eligibility criteria (lines 118-125), and the sources and methods of case ascertainment and control selection (lines 118-125). Give the rationale for the choice of cases and controls
		(*b*) For matched studies, give matching criteria and the number of controls per case NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable - see Methods and Results
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group - see Methods and Results
Bias	9	Describe any efforts to address potential sources of bias - see lines 291-306
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why - see lines 141-156
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding- see lines 141-156
		(*b*) Describe any methods used to examine subgroups and interactions - see lines 141-156
		(*c*) Explain how missing data were addressed - see lines 141-156
		(*d*) If applicable, explain how matching of cases and controls was addressed NA
		(*e*) Describe any sensitivity analyses NA
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed - see lines 158-161
		(b) Give reasons for non-participation at each stage NA
		(c) Consider use of a flow diagram NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – Table 1
		(b) Indicate number of participants with missing data for each variable of interest

Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure – Tables
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – all through Results
		(*b*) Report category boundaries when continuous variables were categorized – See Tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – See Tables and Results
Discussion		
Key results	18	Summarise key results with reference to study objectives – first half of Comment section
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – see lines 291-306
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results – start of Comment
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - reported

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.